Translation

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
C1-A0231P		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/JP2004/000496	21.01.2004	21.01.2003

International Patent Classification (IPC) or national classification and IPC

C12P 21/08, C12N 1/21, C07K 16/00 // C12N 15/09

Applicant

CHUGAI SEIYAKU KABUSHIKI KAISHA

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

3. This report is also accompanied by ANNEXES, comprising:

   a. ☐ *(sent to the applicant and to the International Bureau)* a total of _____ sheets, as follows:

   ☐ sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).

   ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.

   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s))

   _____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
Name and mailing address of the IPEA/	Authorized officer
Facsimile No.	Telephone No.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/JP2004/000496

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on translations from the original language into the following language _____, which is the language of a translation furnished for the purposes of:

☐ international search (Rule 12.3 and 23.1(b))

☐ publication of the international application (Rule 12.4)

☐ international preliminary examination (Rule 55.2 and/or 55.3)

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

☒ the international application as originally filed/furnished

☐ the description:

pages _____ as originally filed/furnished

pages* _____ received by this Authority on _____

pages* _____ received by this Authority on _____

☐ the claims:

nos. _____ as originally filed/furnished

nos.* _____ as amended (together with any statement) under Article 19

nos.* _____ received by this Authority on _____

nos.* _____ received by this Authority on _____

☐ the drawings:

sheets _____ as originally filed/furnished

sheets* _____ received by this Authority on _____

sheets* _____ received by this Authority on _____

☐ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____

☐ the claims, nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/JP2004/000496

Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-7, 10-12	YES
	Claims	8, 9	NO
Inventive step (IS)	Claims	1-7, 10-12	YES
	Claims	8, 9	NO
Industrial applicability (IA)	Claims	1-12	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

Cited documents:

1. Paul Carter, "Bispecific human IgG by design", J Immunol Methods, 2001, vol. 248, pages 7-15
2. WO 98/50431 A2
3. A.M. Merchant *et al.*, "An efficient route to human bispecific IgG", Nat. Biotechnol., 1998, vol.16, no.7, pages 677-681

Documents 1-3 indicate that in order to limit the occurrence of the formation of incorrect combinations of pairs of heavy chains and light chain so that efficient production can be achieved when producing bispecific antibodies having two different heavy chains, a common light chain is used that can be combined with either of the above-mentioned heavy chains. Moreover, when selecting the aforementioned common light chain, a search is performed for an antibody having a light chain comprising an amino acid sequence that is identical to or similar to both the groups of antibodies having one of two heavy chains and the groups of antibodies having the other heavy chain, and the light chain of said antibody is used as the light chain.

Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

Claims 1-7 and 10-12

As indicated above, documents 1-3 disclose the use of a common light chain that can be combined with either of two different heavy chains so that efficient production of bispecific antibodies can be achieved.

However, a method for screening for items fulfilling certain multiple conditions from certain groups, wherein a search is carried out for items fulfilling the first conditions, thereafter a search is carried out among those items obtained in the first search to find items fulfilling the second condition, thereby carrying out sequential screening to obtain items fulfilling multiple conditions, is widely known in this technical field.

As a method for searching for common light chains to use in bispecific antibodies, it would be easy for a person skilled in the art to conceive of replacing the method disclosed in document 1-3 wherein, a search is performed for an antibody having a light chain comprising an amino acid sequence that is identical to or similar to both the groups of antibodies having one of two heavy chains and the groups of antibodies having the other heavy chain, and the light chain of said antibody is used as the light chain, with the method wherein, firstly, a search is performed for light chains that uniquely bond with a desired first antibody by combining with a first heavy chain, and from said light chains, a search is performed for a light chain that uniquely bonds with a desired second antibody by combining with a second heavy chain, hence the light chain ultimately obtained is a common light chain, taking into consideration the technical art at the time of the priority date of the

present application.

However, the application of a screening method, wherein a host cells that secretes a heavy chain is produced, a light chain library is introduced into said host cell, a phage library presenting antibodies constituted by said heavy chains and said light chains is prepared, and a library is selected that presents the antibodies uniquely bonding with a desired antigens, which is used when performing this two-stage screening would not be obvious to a person skilled in the art taking into consideration the technical art at the time of the priority date of the present application.

Since the aforementioned screening method would not be obvious to a person skilled in the art, said screening method characterised wherein the heavy chain is replaced with Fd, and the antibody constituted from a heavy chain and a light chain is replaced with Fab, or wherein based on the gene sequence of the light chain selected using said screening method, a vector is produced that is capable of expressing said light chain and introduced into a host cell, and the host cell is cultured to produce light chains would also not be obvious to a person skilled in the art.

Therefore, the inventions set forth in the above-mentioned claims are inventive in relation to documents 1-3 cited in the international search report.

Claims 8 and 9

The invention set forth in claim 8 is the light chain obtained using the screening method of the invention set forth in claims 1-7. As discussed above,

said screening method is not obvious to a person skilled in the art. However, the light chain obtained using said screening method is a light chain common to two different heavy chains, hence it is impossible to distinguish the difference between this light chain and the common light chains disclosed in documents 1-3.

Similarly, the antibody of the invention disclosed in claim 9 is an antibody containing the light chain obtained using the screening method of the invention set forth in claims 1-7 and it is impossible to distinguish this antibody from the antibody containing a common light chain as disclosed in documents 1-3.

Therefore, the inventions set forth in claims 8 and 9 lack novelty and do not involve an inventive step in the light of documents 1-3 cited in the international search report.